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Occurrence of Monocytoid B Lymphocytes in Lymph Nodes of Patients Treated by Chemotherapy

AKIO OHNISHI, DDS, MASAHIKO OHSAWA, MD, YUTAKA YASUNAGA, MD, NAOKUNI IJUIN, DDS, MASUMI SAWADA, MD, SATORU YAMAMOTO, MD, AND KATSUYUKI AOZASA, MD

From the Departments of Pathology (A.O., M.O., Y.Y., K.A.) and Obstetrics and Gynecology (M.S.), Osaka University Medical School, Osaka, Japan; Department of Pathology, Osaka University Dental School, Osaka (N.I.), Japan; and the Department of Pathology, Kinki Chuo Hospital, Sakai, Japan (S.Y.)

Occurrence of monocytoi B lymphocytes (MBL) in the lymph nodes of patients receiving preoperative chemotherapy for cancer was examined and compared to lymph nodes in controls who had not received chemotherapy. Number of patients receiving and not receiving preoperative chemotherapy were 3 and 10 cases in ovarian cancer, 7 and 11 in testicular cancer, and 22 and 8 in lung cancer, respectively. Chemotherapeutic agents for ovarian, testicular, and lung cancer consisted of cisplatin, Adriamycin, and cyclophosphamide; cisplatin, vinblastine, and bleomycin; and cisplatin, vindesin, and mitomycin, respectively. MBL were defined morphologically as having abundant pale cytoplasm with distinct cell borders and small nucleus. Immunohistochemistry revealed a B-cell nature of these cells, i.e., $CD20^-$ and/or $MB\text{-}1^+$ together with negative reactivity for antibodies for T lymphocytes (CD43, CD45RO, OPD4) and macrophages (KP-1, PGM-1). Monocytoid cells in two cases showed a positive reactivity for CD43 together with CD20. The occurrence rate of MBL in patients with ovarian, lung, and testicular cancer receiving and not receiving chemotherapy was 67% (2/3) and 10% (1/10), 59% (13/22) and 75% (6/8), and 43% (3/7) and 9% (1/11), respectively. The occurrence rate in the total patients receiving chemotherapy (56%) was significantly higher than for those not receiving chemotherapy (28%) ($P < 0.05$). These findings suggest that chemotherapy-induced depressed immune function is causative for the occurrence of MBL in the lymph nodes. MBL might be found more frequently in nodes from patients who have received chemotherapy in certain settings.

KEY WORDS: monocytoid B lymphocytes, cancer, chemotherapy

INTRODUCTION

Monocytoid B lymphocytes (MBL) have pale and abundant cytoplasm and small reniform-shape nuclei, thus mimicking morphologic features of blood monocytes, but immunohistochemical studies have disclosed the distinct B-cell nature of these cells [1]. MBL are known to appear in lymph nodes of patients with toxoplasmic lymphadenitis [1], Sjogren's syndrome [2], cat-scratch disease [3], infectious mononucleosis [4], and acquired immune deficiency syndrome (AIDS) [5]. We recently reported the presence of MBL in the spleen of elderly patients with gastric cancer [6], thyroid gland in Hashimoto's thyroiditis [7], and lymph node affected by

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Address reprint requests to Dr. Katsuyuki Aozasa, Department of Pathology, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka, 565, Japan.

TABLE I. MBL in Lymph Nodes of Patients Treated by Chemotherapy: Histological and Clinical Findings*

Primary site of cancer	Distribution of histologic subtypes	No. of cases	Age (y) (mean)	Sex ratio (M/F)	Stage of disease[a]		
					I	II	III
Ovary							
Chemotherapy (n = 3)	Serous cystadenocarcinoma	2	37–60 (51)	female	0	0	3
	Clear cell carcinoma	1					
No chemotherapy (n = 10)	Serous cystadenocarcinoma	3	39–64 (48)	female	4	5	1
	Endometrioid carcinoma	2					
	Mucinous carcinoma	2					
	Clear cell carcinoma	3					
Testis							
Chemotherapy (n = 7)	Seminoma, embryonal Carcinoma, and/or yolk sac carcinoma	7	26–42 (33)	male	5	2	0
No chemotherapy (n = 11)	Seminoma, embryonal carcinoma, and/or teratocarcinoma	11	19–58 (33)	male	8	3	0
Lung							
Chemotherapy (n = 22)	Large cell carcinoma	7	31–70 (55)	4:1	18	1	3
	Adenocarcinoma	8					
	Squamous cell carcinoma	5					
	Small cell carcinoma	1					
No chemotherapy (n = 8)	Large cell carcinoma	1	51–58 (54)	7:1	8	0	0
	Adenocarcinoma	5					
	Squamous cell carcinoma	2					

*MBL = monocytoid/B lymphocytes.
[a]Stage I = no lymph nodal involvement; Stage II = regional lymph nodal involvement; Stage III = distant lymph nodal involvement.

Hodgkin's disease [8]. These findings suggest that depressed immune function in patients with autoimmune disease, AIDS, and older persons might be responsible for the occurrence of MBL. At present, however, the role of MBL in the immune system is not clear.

Recently we observed the existence of MBL clusters in the abdominal lymph node of patients receiving preoperative chemotherapy for cancer. This suggests that chemotherapy-induced immunosuppression might be a factor for the occurrence of MBL. Therefore, we carried out a systematic study on the occurrence of MBL in lymph nodes of cancer patients receiving chemotherapy.

MATERIALS AND METHODS

Patients

Surgically resected primary tumors and lymph nodes were available in patients with ovarian, testicular, and lung cancers; lymph nodes were obtained from the same anatomic sites in each type of cancer, i.e., pelvic nodes in ovarian and testicular cancer and intrathoracic nodes in lung cancer. Lymph nodes free from cancer metastasis were selected for histologic evaluation of occurrence of MBL. In each type of cancer, patients were divided into two groups, those receiving chemotherapy before surgery and those not. The number of patients receiving and not receiving preoperative chemotherapy were 3 and 10 cases in ovarian cancer, 7 and 11 in testicular cancer, and 22 and 8 in lung cancer, respectively. These patients were admitted to hospitals during the period 1979–93. Histologic classification of cancers, age, sex ratio, and stage of disease are shown in Table I. There were no prominent differences between patients receiving and not receiving chemotherapy in each type of cancer except for having rather advanced disease in patients with ovarian cancer receiving chemotherapy. Chemotherapeutic agents for ovarian, testicular, and lung cancer consisted of cisplatin, Adriamycin, and cyclophosphamide; cisplatin, vinblastine, and bleomycin; and cisplatin, vindesin and mitomycin, respectively.

Histologic specimens were fixed in 10% formalin and routinely processed for paraffin-embedding. Sections, cut at 4 μm, were stained with hematoxylin and eosin and immunoperoxidase procedures (ABC method). The monoclonal antibodies used in this study and their reactivity and suppliers are listed in Table II. Mean numbers of lymph nodes studied for the presence of MBL in ovarian, testicular, and lung cancer with or without chemotherapy was 9 and 7, 4 and 10, and 10 and 7, respectively. Three pathologists (AO, MO, KA) participated in the classification of MBL: they discussed to reach a consensus when they had different judgments.

Statistical Analysis

The significance of the difference in the frequency of occurrence of the MBL between patients with and without chemotherapy was evaluated by Chi-square tests with Yates' correction.

RESULTS

Monocytoid cells were defined morphologically as having abundant pale cytoplasm with a distinct cell border. Their small nuclei showed a vesicular chromatin pattern, often with reniform shape. These cells presented as irregularly shaped collections of cells surrounding a mantle zone, or in some cases, directly adjoining the

TABLE II. Antibody Panel

Antibody	Primary immunoreactivity	Source
CD3	T cells	Dakopatts (Copenhagen, Denmark)
CD15(LeuM1)	Monocytes, myeloid cells, some epithelioid cells	Beckton Dickinson (Mountain View, CA)
CD20(Mx-panB)	B cells	Kyowa Medex (Tokyo, Japan)
CD30(Ber-H2)	Reed-Sternberg cell-associated antigen	Dakopatts
CD43(MT-1)	T cells	Bioscience (Emmenbruke, Switzerland)
CD45RO(UCHL-1)	T cells	Dakopatts
MB-1	B cells	Bioscience
KP-1	Monocytes, granulocytes	Dakopatts
PGM1	Monocytes	Dakopatts

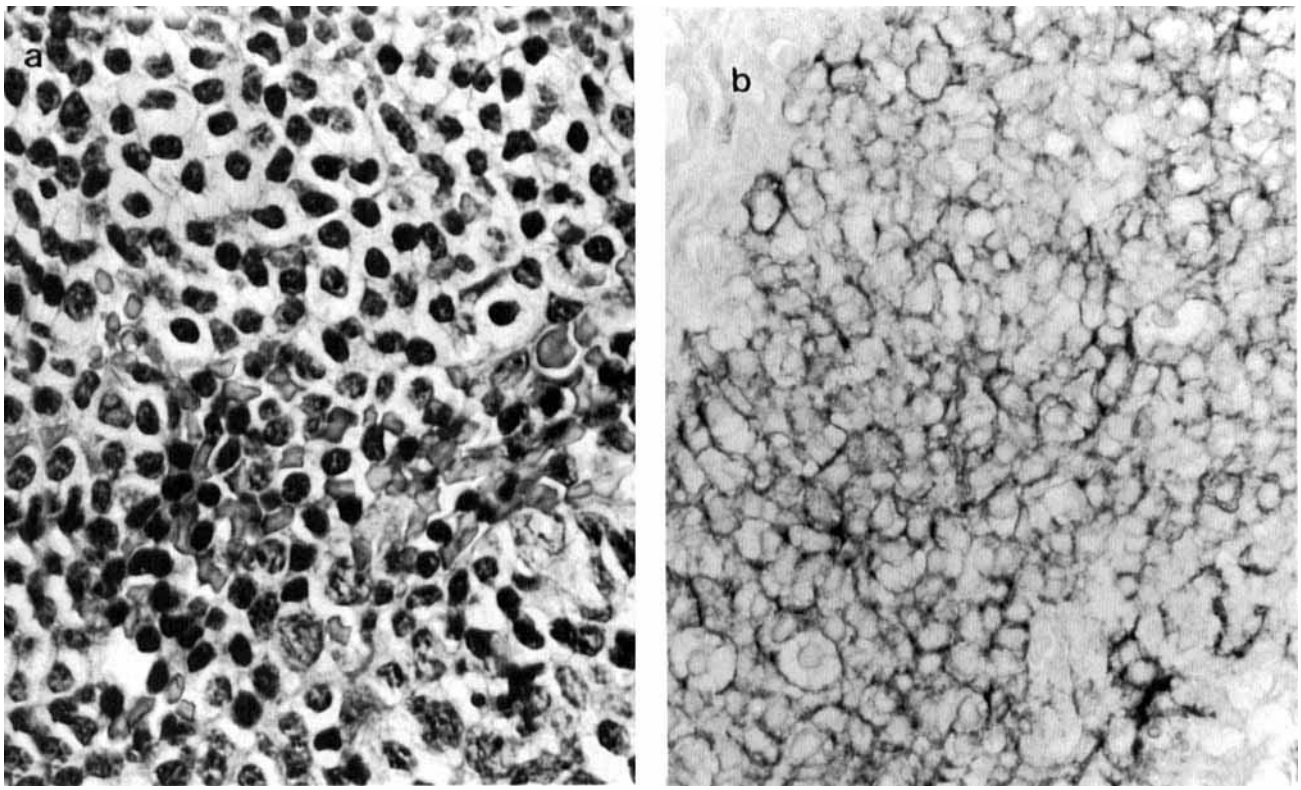

Fig. 1. **(a)** Monocytoid cells surrounding the secondary lymph follicle. (lower right) H. E. ×750 **(b)** These cells showed positive reaction for CD20. ABC method ×700.

secondary follicles of lymph follicles (Fig. 1). Immunohistochemistry revealed that these were B cells with the following profile of antigen expression: CD20 positive in almost all cases, MB-1 positive in about half of cases, and CD45RO, OPD4, LeuM1, KP-1, and PGM-1 negative in all cases. Monocytoid cells in two cases showed a positive reactivity for CD 43 together with CD20. In the lymph nodes without MBL, both the mantle zone and secondary follicle were distinct with occasional hyperplasia found in the secondary follicles. In the lymph nodes with MBL, the mantle zone frequently showed atrophy with or without atrophy of the secondary follicles.

Frequency of occurrence of MBL in each type of cancer with or without chemotherapy is shown in Table III. In MBL positive cases, MBL were found in more than a half of lymph nodes examined. The occurrence rate in the total patients receiving chemotherapy (56%) was significantly higher than for those not receiving chemotherapy (28%) ($P < 0.05$).

DISCUSSION

MBLs could appear in the parafollicular area of lymph nodes; therefore, the term "parafollicular B lymphocytes" was proposed [9]. In the present series of patients, the

TABLE III. Occurrence of Monocytoid B Lymphocytes in Cancer Patients With or Without Chemotherapy

Primary sites	Chemotherapy	No chemotherapy
Ovary	2/3*	1/10*
Lung	13/22*	6/8*
Testis	3/7*	1/11*

MBLs appear in the parafollicular area of lymph node, not in the sinus as usually seen in toxoplasmic lymphadenitis [1,4]. Recently we reported the occurrence of MBL in spleen of patients with gastric cancer and suggested transformation of the marginal zone lymphocytes to MBL through detailed microscopic observation [6]. These findings suggest superficial resemblance of parafollicular cells in the lymph node and parafollicular cells in the spleen. Cousar et al. [10], however, were against this opinion.

The monocytoid cells in the present series showed a positive reactivity for antibodies against B lymphocytes but negative for those against T lymphocytes, indicating a B-cell nature. Monocytoid cells in two cases showed a positive reactivity for CD43, an antibody directed for T lymphocytes. However, the B-cell nature of the monocytoid cells in these two cases was evident because of $CD20^-$, $CD45RO^-$, and, $OPD4^-$. Positive immunoreactivity of monocytoid cells with CD43 was also found in the thyroid gland of a few patients affected by Hashimoto's disease [7].

Previous study suggested that depressed immune function might be responsible for the occurrence of MBL [2,5–8]. The current results showed the higher frequency of occurrence of MBL in patients receiving chemotherapy than those without ($P < 0.05$). These findings showed that MBL might be found more frequently in nodes from patients who have received chemotherapy in certain settings. In patients with ovarian cancer, advanced disease might be causative for more frequent finding of MBL. In patients with lung cancer, chemotherapy did not affect the frequency of the occurrence of MBL, although the frequency itself, even in patients not receiving chemotherapy, was rather higher than in patients with testicular cancer. Depressed immune function or other factors that exist before chemotherapy might render the occurrence of MBL in patients with lung cancer.

A malignant counterpart of MBL has been recognized, and the term "monocytoid B-cell lymphoma" (MBCL) proposed for this disease [11]. MBCL is relatively common among thyroid lymphoma and gastric lymphoma [12,13]. Etiologic importance of Hashimoto's disease, an organ-specific autoimmune disease in the thyroid gland, for development of thyroid lymphoma is well known [14,15]. Recent pathologic [16] and epidemiologic studies [17] suggested that Helicobacter pylori infection, by inducing lymphoid tissue in gastric mucosa, is a necessary precursor for the development of gastric lymphoma. Indeed, autoimmunity is also postulated to play a role in Helicobacter gastritis [18]. These findings support the present conclusion that immune deficiency is a factor for the occurrence of MBL.

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